REMARKS

Entry of the Amendment and reconsideration of the claims is respectfully requested. A Notice of Appeal is also submitted herewith. Applicant submits the Amendment places the claims in better form for consideration on appeal and the Remarks further clarify the issues for appeal. Applicant requests an interview be granted prior to submission of the appeal brief in hopes that prosecution can be advanced.

Claims 28-43 are new. After entry of the Amendment, claims 23-43 will be pending. Applicant submits the Amendment raises no issues of new matter. New claims 28-43 are supported throughout the specification, including for example at page 12, line 24 to page 13, line 3, at page 11, lines 5-10, and at page 15, lines 6-12, lines 14-15, and lines 17-21.

Enablement

Claims 23-27 were rejected under 35 U.S.C. § 112, first paragraph, as lacking enablement. Applicant respectfully traverses the rejection.

(1) The state and predictability of the art.

The Examiner alleges the claimed invention falls within the realm of gene therapy and is therefore not enabled because gene therapy is an immature and highly unpredictable art as evidenced by Orkin (Report and Recommendations of the Panel to Assess the NIH Investigation in Research on Gene Therapy, NIH, December 7, 1995) and/or Dang et al. (1999, Clin. Cancer Res., 5:471-474). Applicant respectfully disagrees.

The references cited by the Examiner discuss difficulties associated with gene therapy methods for treating genetic diseases. Applicant's claims, however, are directed to methods of treating an ocular wound with a viral expression vector comprising a nucleic acid encoding a polypeptide useful for treating the wound. Neither Orkin nor Dang et al. discuss gene therapy treatments for an ocular disease or ocular wound. None of the clinical trials cited in table 1 in Orkin are directed to treating a wound or disease in an ocular tissue. None of the clinical trials or research discussed in Dang et al. are directed to treating a wound or disease in an ocular tissue. Therefore, none of the difficulties highlighted in the cited references for treating genetic disease are applicable to the claimed invention.

Furthermore, Orkin and Dang et al. discussed difficulties associated with gene therapy treatments for treating genetic disease in the context of clinical trials and achieving clinical efficacy. However, clinical safety and efficacy is not the standard by which patentability is assessed. Considerations made by the FDA in determining safety and efficacy in the context of a clinical trial are different from those made by the USPTO in determining whether a claim is enabled (MPEP § 2164.05). The claimed invention is fully enabled.

Citing Bennett and Maguire (2000, Mol. Ther., 1:501-505), the Examiner asserts the difficulties traditionally associated with gene therapy are the same difficulties encountered in the art of ocular gene therapy. Applicant respectfully disagrees.

Orkin recognized that each individual gene therapy protocol must be analyzed in the context of the problem being addressed and the specifically proposed gene therapy based solution.

> The types of diseases under consideration for gene therapy are diverse; hence, many different strategies are being investigated, each with its own set of scientific and clinical challenges. Orkin et al., Report and Recommendations of the Panel to Assess the NIH Investigation in Research on Gene Therapy, NIH, December 7, 1995 at page 1.

Many of the difficulties associated with gene therapy methods for treating a genetic disease, such as suboptimal vectors, lack of stable *in vivo* transgene expression, low frequency of gene transfer, lack of suitable controls, and lack of defined endpoints, as discussed by Orkin and Dang et al., are not difficulties in the context of gene therapy methods for treating a wound in ocular tissue. Compared to other tissues, the eye is an easily accessible target for gene therapy. Gene transfer and transgene expression in ocular tissues can be observed and monitored directly, as known in the art.

> Because standard ophthalmologic equipment, that is, the slit-lamp bimicroscope, allows one to visualize the cornea and surrounding tissues under high magnification and determine transfection success and safety, these methods can be readily transferred from the laboratory to the clinic. Stechschulte et al., 2001, Invest. Ophthalmol. Vis. Sci., 42:1975-1979 at page 1978, second column.
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> Moreover, success or failure of gene delivery in the cornea can be monitored visually in live animals by tagging fluorescent gene markers, such as enhanced green fluorescent protein (EGFP), to the test gene. Mohan et al., 2005, Prog.

> Retinal Eye Res., pages 1-20, electronically published at www.sciencedirect.com on June 11, 2005 at page 2, first column (Exhibit 1).

Delivery routes for a viral gene therapy vector to an ocular tissue, such as microinjection, subconjunctival injection, or topical application, allow for localized exposure of the target ocular tissue with reduced risk of systemic effects. (Cordeiro et al., 1999, Br. J. Ophthalmol., 83:1219-1224 at page 1221, second column). Consequently, a subject's eyes can be treated individually allowing the untreated eye to be utilized an as internal control (Bennett and Maguire, 2000, Mol. Ther., 1:501-505 at page 504, second column). In the context of an ocular wound, for example, gene transfer efficiency and transgene expression can be monitored by visually observing the progression and rate of wound healing compared to a control and/or visually monitoring transgene expression via a reporter gene.

The specification provides methods for introducing an exogenous nucleic acid into an ocular cell such that the cell expresses the exogenous nucleic acid. The exogenous nucleic acid can encode a variety of polypeptides, including a reporter polypeptide (such as β-galactosidase) or a therapeutically useful polypeptide (such as TGF-β). The Examples demonstrate viral vectors efficiently deliver nucleic acids to ocular cells. Using a reporter gene, Applicant shows ocular cells express the reporter transgene at a level sufficient to result in measurable expression of the polypeptide (Examples 1-3). Measurable expression of a reporter gene product (β-galactosidase) was shown in corneal epithelial cells, corneal endothelial cells, and choroid cells (Figures 1A and 2A).

Subsequent publications confirm Applicant's teachings. Viral vectors such as adenovirus, adeno-associated virus, and lentivirus have been shown to efficiently deliver genes to ocular cells.

> As with any gene therapy experiment, success in the eye is dictated by the ability to efficiently transfer genetic material to target cells and to achieve long-term expression at appropriate levels. Recombinant viruses have been used most successfully for this purpose. Utility of each of the different viruses varies according to the target cell type. <u>As shown in Table 1, viruses that have proven useful for delivery to ocular cells include recombinant adenovirus (Ad), adeno-associated virus (AAV), and lentivirus (HIV).</u> Bennett and Maguire, 2000, Mol. Ther., 1:501-505 at page 501, second column (emphasis added).

> [Gene transfer studies performed by many investigators] have demonstrated that candidate genes can be delivered into all three major cell types of the cornea in vivo using both viral and non-viral methods. Viral methods are capable of delivering genes at high efficiency for longer period of time compared to the non-viral methods. Mohan et al., 2005, Prog. Retinal Eye Res., pages 1-20, electronically published at www.sciencedirect.com on June 11, 2005 at page 18, second column (Exhibit 1).

In view of the transduction efficiency and measurable reporter gene expression shown by Applicant in ocular cells, one of skill in the art would reasonably expect transduced ocular cells to express a transgene at a therapeutically useful level. Subsequent publications confirm measurable expression of a reporter gene in cells transduced with a viral expression vector correlates with therapeutically useful expression of an exogenous nucleic acid encoding a polypeptide having a therapeutic activity in cells transduced with the same viral expression vector. Several studies have demonstrated that ocular cells infected by viral vectors express the delivered exogenous nucleic acid(s) at therapeutically useful levels *in vivo*. Adenovirus-mediated delivery of rhodopsin-promoted *bcl-2* to retinal cells delayed photoreceptor death in rd/rd mice (Bennett et al., 1998, Gene Ther., 5:1156-1164). The adenovirus-mediated gene transfer resulted in photoreceptor rescue that persisted for approximately 6 weeks (Bennett et al., 1998, Gene Ther., 5:1156-1164, at page 1159, second column). In another study, retroviral-mediated delivery of a thymidine kinase gene to corneal cells resulted in a significant reduction in corneal haze following superficial keratectomy. (Seitz et al., 1998, Am. J. Ophthamol., 126:630-639 (Exhibit 2)). In yet another study, retrovirus-mediated delivery of a dominant-negative cyclin G1 to corneal cells after transepithelial phototherapeutic keratectomy markedly reduced the development of corneal haze (Behrens et al., 2002, Invest. Ophthalmol. Vis. Sci., 43:968-977 (Exhibit 3)).

Moreover, ocular cells transduced by non-viral vectors, which have reduced transduction efficiency in ocular cells as compared to viral vectors, also express the delivered nucleic acid(s) at therapeutically useful levels *in vivo*. Cornea cells transduced *in vivo* with naked DNA encoding vascular endothelial growth factor (VEGF) induced corneal neovascularization, iris vascular engorgement, and hyphema in mouse eyes (Stechschulte et al., 2001, Invest. Ophthalmol. Vis. Sci., 42:1975-1979 at page 1978, first column). Also, corneal injection of

naked DNA encoding a soluble form of the VEGF receptor FLT-1 effectively prevented VEGF-induced corneal neovascularization *in vivo* (Stechschulte et al., 2001, Invest. Ophthalmol. Vis. Sci., 42:1975-1979, at page 1978, first column).

The Examiner further alleges qualitative detection of β-galactosidase expression in ocular cells is not reasonably correlated to the claimed therapeutic effects. The Examiner asserts an effective or appropriate level of a therapeutic protein must be expressed to yield the desired therapeutic effects and there is no evidence, either in the specification or prior art, that *in vivo* transgene expression can be properly controlled to achieve the desired therapeutic levels. Applicant respectfully disagrees.

The specification shows that a viral vector, such as an adenoviral vector, can be used to practice the claimed invention by demonstrating measurable expression of a reporter gene and disclosing that the reporter gene can be substituted with a nucleic acid encoding a therapeutic polypeptide. Measurable expression of a reporter gene in cells transduced with a viral expression vector correlates with therapeutically useful expression of a nucleic acid in cells transduced with a viral expression vector encoding a polypeptide having a therapeutic activity. The concentration of viral vector necessary to achieve a therapeutic level of polypeptide expression could be determined without undue experimentation using the guidance provided in the specification and knowledge in the art. Subsequent publications confirm Applicant's disclosure. For example, Bennett et al. observed therapeutic effects with a dosage of $2.5x10^7$ pfu, similar to the dosage taught by Applicant (20 μl of a $1x10^9$ pfu/ml solution = $2x10^7$ pfu; see Examples 1-3).

The Office Action alleges the "specification is not enabled for the instant invention because at the effective filing date of the present application (October 31, 1994), gene therapy was an immature and highly unpredictable art" (Office Action at page 4). In view of the forgoing, Applicant respectfully disagrees. Both Orkin and Dang et al. addressed difficulties associated with gene therapy in the context of clinical trials and achieving clinical efficacy for treating a genetic disease. Many of the issues associated with gene therapy methods in the context of treating a genetic disease are not issues in the context of treating a wound in ocular tissue. For example, Applicant has shown that viral vectors efficiently deliver nucleic acids to

ocular cells and that ocular cells express the delivered nucleic acid at a level of measurable expression. Withdrawal of this rejection is respectfully requested.

(2) The breadth of the claims.

Applicant submits the specification sufficiently enables the breadth of the claims.

(3) The amount of direction or guidance presented.

The Examiner alleges the specification lacks specific guidance or relevant *in vivo* examples demonstrating any beneficial wound healing effect anywhere in the eye, and therefore lacks enablement. Applicant respectfully disagrees.

Applicant does not need to describe all actual embodiments to satisfy the enablement requirement (MPEP § 2164.02). An example is not necessary if the invention is otherwise disclosed in such a manner that one skilled in the art would be able to practice it without an undue amount of experimentation (MPEP § 2164.02).

As discussed above, Applicant discloses methods of delivering an exogenous nucleic acid using viral vectors into ocular cells such that cell expresses the exogenous nucleic acid (Examples 1-3). The specification discloses using viral vectors to deliver to ocular cells an exogenous nucleic acid encoding a polypeptide useful for treating an ocular wound (see specification, for example, at page 15, lines 6-12). The specification provides TGF-β, a growth factor, as one example of such a useful polypeptide (see specification, for example, at page 15, lines 14-15). At the time of filing, growth factors were known to enhance healing of ocular wounds. Topical application or intraocular injection of growth factor polypeptides, such as TGF-β (WO9401124 (Exhibit 4); Glaser et al., 1992, Ophthalmol., 99:1162-1173), epidermal growth factor (Tripathi et al., 1990, Cornea, 9:2-9 (Exhibit 5)), fibroblast growth factor (Tripathi et al., 1990, Cornea, 9:2-9 (Exhibit 5)), mesodermal growth factor (Tripathi et al., 1990, Cornea, 9:2-9 (Exhibit 5)), or keratinocyte growth factor (Sotozono et al., 1995, Invest. Ophthalmol. Vis. Sci., 36:1524-1529 (Exhibit 6)) had been shown to enhance healing of ocular wounds, including macular holes and corneal wounds. In view of Applicant's teachings, one of skill in the art would have been able to use a nucleic acid in the methods of the invention encoding any of the growth factors known to enhance wound healing in ocular tissue without undue experimentation.

Withdrawal of this rejection is respectfully requested.

Citing Cordeiro et al. (1999, Br. J. Ophthalmol., 83:1219-1224), the Examiner alleges modulating the wound healing process to attain a beneficial therapeutic effect is not routine as the wound healing process involves many complex molecular and cellular events. Applicant respectfully disagrees. At the time of filing, topical application and intraocular injection methods for healing ocular wounds, such as for example corneal wounds (Tripathi et al., 1990, Cornea, 9:2-9 (Exhibit 5); Sotozono et al., 1995, Invest. Ophthalmol. Vis. Sci., 36:1524-1529 (Exhibit 6)) or macular holes (WO9401124 (Exhibit 4)) with growth factor polypeptides, such as epidermal growth factor, keratinocyte growth factor, or TGF-β, were known. Therefore, one of ordinary skill in the art would have been able to modulate the wound healing process without undue experimentation.

Withdrawal of this rejection is respectfully requested.

The Examiner alleges it is unclear what proteins would be useful in the treatment of ocular wounds and which ocular cells should be contacted in order to attain the desired effect. Applicant respectfully disagrees.

The specification discloses delivering to ocular cells an exogenous nucleic acid encoding a polypeptide useful for treating an ocular wound. The specification provides growth factors such as TGF-β as one example of such a useful polypeptide. At the time of filing, growth factors such as TGF-β, epidermal growth factor, fibroblast growth factor, mesodermal growth factor, insulin-like growth factor, and keratinocyte growth factor were known to enhance healing of ocular wounds.

In view of Applicant's teachings and the prior art, one of skill in the art would have been able to determine which cells should be contacted to treat a specific ocular wound without undue experimentation. At the time of filing, the structure of the eye was well defined and a variety of perforating and non-perforating ocular wounds, including corneal wounds, corneal ulcers, macular holes, and choroidretinal rupture, had been characterized. The specification shows expression of an exogenous nucleic acid in corneal epithelial cells, corneal endothelial cells, and choroid cells using the methods of the invention.

Withdrawal of this rejection is respectfully requested.

The Examiner alleges the specification does not provide any guidance regarding how to control expression of TGF-β in ocular cells such that scarring and degeneration of ocular tissues does not occur. Applicant respectfully submits that review of the claims by the Patent Office is confined to the statutory requirements of the patent law. The claims are directed to methods of healing ocular wounds. Whether scarring or degeneration is or is not a side effect of the claimed treatment methods is not relevant to satisfying the enablement requirement. Other governmental agencies, such as the FDA, have been assigned the responsibility of ensuring the safety of gene therapy methods (see for example MPEP § 2164.05).

Moreover, concentrations of TGF-β2 (a species of TGF-β) that promote flattening of macular holes do not induce excessive fibrosis or proliferative vitreoretinopathy. For example, WO9401124 (Exhibit 4) discloses 330 to 1330 ng of TGF-β2 flattens macular holes and promotes formation of fibrous tissue along the margin of the macular holes, which is associated with visual recovery (WO9401124 at page 29, lines 2-10). A major concern in this study was that TGF-β2 might cause excessive fibrosis, which can increase macular contraction and result in proliferative vitreoretinopathy. However, the concentrations of TGF-β2 (330 to 1330 ng) that effectively promoted flattening of macular holes was significantly less than the concentration of TGF-β2 in eyes with proliferative vitreoretinopathy (WO9401124 at page 29, lines 31-34). None of the 60 eyes treated with TGF-β2 developed excessive fibrosis or proliferative vitreoretinopathy (WO9401124 at page 29, lines 34-37).

Withdrawal of this rejection is respectfully requested.

In summary, the specification provides sufficient guidance and direction to practice the claimed methods without undue experimentation. The specification discloses methods for treating an ocular wound comprising introducing an exogenous nucleic acid via a viral vector into an ocular cell such that the cell expresses the exogenous nucleic acid. The exogenous nucleic acid can encode a variety of polypeptides, including a reporter polypeptide (such as β-galactosidase) or a therapeutically useful polypeptide (such as TGF-β). Measurable expression of a reporter gene product (β-galactosidase) was shown in different ocular cell types, including corneal epithelial cells, corneal endothelial cells, and choroid cells (Figures 1A and 2A). Subsequent studies confirm Applicant's teaching that viral vectors efficiently transduce ocular

cells and express measurable amounts of a reporter gene in cells transduced with the viral expression vector. Expression of the exogenous reporter nucleic acid correlates with therapeutically useful expression of an exogenous nucleic acid in cells transduced with a viral expression vector encoding a polypeptide having a therapeutic activity. Accordingly, withdrawal of the enablement rejection is respectfully requested.

Conclusion

In view of the above Amendment and Remarks, Applicant respectfully requests entry of the Amendment and a Notice of Allowance. Applicant notes a Notice of Appeal is submitted herewith and requests an interview be granted prior to submission of the appeal brief in hopes that prosecution can be advanced. The undersigned attorney can be contacted using the information shown below.

Respectfully submitted,

MERCHANT & GOULD P.C.
P.O. Box 2903
Minneapolis, Minnesota 55402-0903
(612) 332-5300

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Denise M. Kettelberger
Reg. No. 33,924
612.371.5268 (direct)
dkettelberger@merchant-gould.com